IN THE CLAIMS:

Please enter the following cancellations, amendments and/or additions as follows:

Claim 1. (Cancelled).

Claim 2. (Previously Presented) The method as claimed in Claim 9, wherein said antibiotic in step (b) is selected from the group consisting of rifampicin, kanamycin, ampicillin and pyrazinamide.

Claim 3. (Currently Amended) The method as claimed in Claim 9, wherein in step (b) said concentration of said at least one antibiotic is 25 to 150 μg/ml and said dormant ~~phase~~ culture contain 10^5 to 10^9 bacteria//ml.

Claim 4. (Previously Presented) The method as claimed in Claim 9, wherein said bacterial strain is selected from a strain in the group consisting of the species *Staphylococcus aureus*, *Escherichia coli*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Streptococcus gordonii* and *Mycobacterium tuberculosis*.

Claim 5. (Previously Presented) The method as claimed in Claim 9, wherein said bacterial strain is a strain of the species *Mycobacterium tuberculosis* and said antibiotic in step (b) is rifampicin.

Claim 6. (Previously Presented) The method as claimed in Claim 9, wherein said bacterial strain is a strain of the species *Escherichia coli* and said antibiotic in step (b) is kanamycin.

Claim 7. (Previously Presented) The method as claimed in Claim 9, wherein said bacterial strain is a strain of the

species *Staphylococcus aureus* and said antibiotic in step (b) is ampicillin.

Claim 8. (Cancelled).

Claim 9. (Currently Amended) A method for identifying whether a test compound has antibacterial activity against dormant bacteria comprising the steps of:

(i) preparing a phenotypically antibiotic-resistant subpopulation of dormant bacteria according to the method comprising at least the steps of:

(a) growing an antibiotic-sensitive bacterial strain to stationary phase to obtain a dormant culture; and

(b) treating the resulting dormant culture with at least one antibiotic at a concentration and for a time sufficient to kill growing bacteria of said strain, and selecting a phenotypically antibiotic-resistant subpopulation;

(ii) incubating a sample of said phenotypically antibiotic-resistant subpopulation with said test compound; and

(iii) assaying whether said test compound exhibits any antibacterial activity against said phenotypically antibiotic-resistant subpopulation so as to identify whether said test compound has any antibacterial activity against said dormant ~~phase~~ bacteria.

Claim 10. (Previously Presented) The method according to Claim 9, further comprising the step of amplifying said test compound.

Claims 11-19. (Cancelled)

REMARKS

In the Advisory Action dated August 21, 2003, the Examiner refuses to enter the Amendment After Final filed July 23, 2003, because, *inter alia*, the Examiner contends that such raises new issues which require further search and/or consideration.

Specifically, in the attachment to the Advisory Action, the Examiner contends that replacing "stationary phase culture" with "dormant", and the deletion of "or a composition comprising said test compound" and the optional isolating step raise new issues and new matter.

Applicants respectfully submit that these amendments do not raise new matter for the reasons set forth in the Amendment After Final, i.e., the specification refers to dormancy. Further, deletion of the composition phrase and the optional isolation step, do not constitute new matter, and are fully supported by the present application.

The Examiner also contends that there is insufficient antecedent basis in Claim 9 for "said dormant phase bacteria" in the last line, and in Claim 3 regarding "said dormant phase culture".

In view of the amendments herein to Claim 3 to refer to "said dormant culture", and Claim 9, last line, to delete "phase", Applicants respectfully submit that the Examiner's objection has been rendered moot.

On page 2 of the Advisory Action, the Examiner contends that Yu et al does not teach that the definition of "genotypic" and "phenotypic" resistance pertains to bacteria other than *Mycobacterium tuberculosis*.

Further, the Examiner states that Yu et al is not probative of a definition generally used in the art, i.e., two of the authors of Yu et al are inventors of the present application, and the priority date of the present application is prior to the publication date of Yu et al.

Applicants submit herewith copies of additional references (Boswell et al, *J. Antimicrob. Chemother.*, 39 (Suppl. A):29-32 (1997); Entenza et al, *J. Infect. Dis.*, 175(1):70-76 (1997); Entenza et al, *J. Infect. Dis.*, 170(1):100-109 (1994); and Tuomanen et al, *Scand. J. Infect. Dis. Suppl.*, 74:102-112 (1990)) from another research group which demonstrate the art-recognized definitions of "genotypic" and "phenotypic" resistance as they pertain to bacteria in general.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration, and allowance are requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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23373
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Date: September 23, 2003

J Antimicrob Chemother. 1997 May;39 Suppl A:29-32.

Time-kill kinetics of quinupristin/dalfopristin on Staphylococcus aureus with
and without a raised MBC evaluated by two methods.

Boswell FJ, Sunderland J, Andrews JM, Wise R.

Department of Medical Microbiology, City Hospital NHS Trust, Birmingham, UK.

Some strains of staphylococci have raised MBCs of quinupristin/dalfopristin
compared with their MICs. In this study, the time-kill kinetics of quinupristin/dalfopristin at 2 mg/L on two strains of Staphylococcus aureus were
determined by viable count and intracellular ATP measurement. After 24 h
exposure to quinupristin/dalfopristin, the percentage survival of the strain
with a raised MBC was 5.9 and that of the strain with a normal MBC was 0.04. The
time-kill kinetics of the strain with a raised MBC were analogous to those
associated with phenotypic tolerance.

PMID: 9511059 [PubMed - indexed for MEDLINE]

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J Infect Dis. 1997 Jan;175(1):70-6.

Importance of genotypic and phenotypic tolerance in the treatment of experimental endocarditis due to Streptococcus gordonii.

Entenza JM, Caldelari I, Glauser MP, Francioli P, Moreillon P.

Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois,
Lausanne, Switzerland.

Genotypic and phenotypic tolerance was studied in penicillin treatment of
experimental endocarditis due to nontolerant and tolerant Streptococcus gordonii
and to their backcross transformants. The organisms were matched for in vitro
and in vivo growth rates. Rats with aortic endocarditis were treated for 3 or 5
days, starting 12, 24, or 48 h after inoculation. When started at 12 h, during
fast intravegetation growth, 3 days of treatment cured 80% of the nontolerant
parent compared with <30% of the tolerant derivative ($P < .005$). When started at
24 or 48 h and if intravegetation growth had reached a plateau, 3 days of
treatment failed against both bacteria. However, a significant difference

between the 2 organisms was restored when treatment was extended to 5 days.
Thus, genotypic tolerance conferred a survival advantage in both fast- and
slow-growing bacteria, demonstrating that the in vitro-defined tolerant
phenotype also carried the risk of treatment failure in vivo.

PMID: 8985198 [PubMed - indexed for MEDLINE]

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J Infect Dis. 1994 Jul;170(1):100-9.

Antibiotic treatment of experimental endocarditis due to methicillin-resistant
Staphylococcus epidermidis.

Entenza JM, Fluckiger U, Glauser MP, Moreillon P.

Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois,
Lausanne, Switzerland.

The natural history and treatment of experimental endocarditis due to heterogeneous and homogeneous methicillin-resistant Staphylococcus epidermidis
was investigated. Amoxicillin/clavulanate or vancomycin were administered for 3
days via a computerized pump to mimic human drug kinetics in animals. After
challenge with the minimum inoculum producing 90% of infections (ID90), bacteria
in the vegetations grew logarithmically for 16 h. Then, bacterial densities
stabilized (at approximately 10(8) cfu/g) and growth rates sharply declined.
Both regimens cured > or = 60% of endocarditis (due to heterogeneous or
homogeneous bacteria) when started 12-16 h after infection, although the
bacterial densities in the vegetations had increased by 20 times in between. In
contrast, treatment started after 24 h failed in most animals, while bacterial
densities had not increased any more. Thus, while both regimens were equivalent,
the therapeutic outcome was best predicted by growth rates in the vegetations,
not by bacterial densities. These observations highlight the importance of
phenotypic tolerance developing in vivo.

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Scand J Infect Dis Suppl. 1990;74:102-12.

Mechanism of phenotypic tolerance of nongrowing pneumococci to beta-lactam
antibiotics.

Tuomanen E, Tomasz A.

Rockefeller University, New York, New York.

Within minutes after the onset of deprivation of an essential nutrient, all bacteria develop resistance to lysis by beta-lactam antibiotics, a phenomenon termed phenotypic tolerance. Two phases of this process were identified in pneumococci and the activity of the major autolysin, an N-acetylmuramyl-L-alanine amidase, was studied in each phase. Autolysin was detectable by immunofluorescence in a uniform distribution over the surface of growing pneumococci, but became progressively depleted during amino acid deprivation. Lysis of nongrowing cells by beta-lactam antibiotics could be reconstituted by addition of exogenous autolysin during the first 80 minutes of starvation (Phase I) but not thereafter (Phase II). Similarly, Triton X-100 or deoxycholate lysed nongrowing cells in Phase I but not Phase II. Cell wall isolated from Phase II cells was found to be more resistant to hydrolysis by the autolysin in vitro than that from growing cells. Lysis of growing cells could also be inhibited by incorporation of a pulse of nonhydrolysable cell wall or autolysin deficient cell wall into the growth zone. These results suggest that phenotypic tolerance in nongrowing pneumococci involves rapid loss or disengagement of autolysin molecules from their in situ attack-sites (Phase I) followed by a second slower process that involves a progressive change in the cell wall structure to a form less susceptible to hydrolysis by the autolysin (Phase II).

PMID: 1982975 [PubMed - indexed for MEDLINE]